

EXHIBIT A

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THE MERCK MANUAL

SEVENTEENTH
EDITION

CENTENNIAL EDITION

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FOREWORD

With this edition, *The Merck Manual* celebrates its 100th birthday. When the editors of the 1st Edition produced their 192-page compendium, they could not have realized the extent to which medical knowledge would explode over the next century. *The Merck Manual* now fills 2,656 pages and covers countless diseases that were not known 100 years ago. A brief review of medical practice as reflected in *The Merck Manual* during the past century follows on page vii.

Although the knowledge of medicine has grown, the goal of *The Merck Manual* has not changed—To provide useful clinical information to practicing physicians, medical students, interns, residents, nurses, pharmacists, and other health care professionals in a concise, complete, and accurate manner. *The Merck Manual* continues to cover all the subjects expected in a textbook of internal medicine as well as detailed information on pediatrics, psychiatry, obstetrics, gynecology, dermatology, pharmacology, ophthalmology, otolaryngology, and a number of special subjects. *The Merck Manual* quickly provides information that helps practitioners achieve optimal care. The more specialized the practice of medicine becomes, the more important such information becomes. Specialists as well as generalists must at some time quickly access information about other specialties.

The 17th edition of *The Merck Manual* is the culmination of an arduous but rewarding 7-year enterprise. Every topic has been updated, and many have been completely rewritten. Topics new to this edition include hand disorders, prion diseases, death and dying, probabilities in clinical medicine, multiple chemical sensitivity, chronic fatigue syndrome, rehabilitation, smoking cessation, and drug therapy in the elderly, among others. The members of the Editorial Board, special consultants, and contributing authors are listed on the following pages with their affiliations. They deserve a degree of gratitude that cannot be adequately expressed here, but we know they will feel sufficiently rewarded if their efforts serve your needs.

Because of the extensive subject matter covered and a successful tradition developed through trials of successes and failures, *The Merck Manual* has some unique characteristics. We urge readers to spend a few minutes reviewing the Guide for Readers (p. xii), the Table of Contents at the beginning of each section (indicated by a thumb tab), and the Index (p. 2657). Subject headings within each section, internal headings within a subject discussion, and boldfaced terms in the text form an outline intended to help with use of the text.

We hope this edition of *The Merck Manual* will serve as an aid to you, our readers, compatible with your needs and worthy of frequent use. Suggestions for improvements will be warmly welcomed and carefully considered.

Mark H. Beers, M.D., and Robert Barrow, M.D., Editors

LOGIC DISORDERS

CHAPTER 116 - DISORDERS OF HAIR FOLLICLES AND SEBACEOUS GLANDS / 811

OF WART VIRUS AND CLINICAL CORRELATIONS

Human papillomavirus Type	Clinical Correlations
1, 7	Benign
1	Benign
18, 33	Of women, 28% have associated cervical dysplasia with koilocytic cells
18, 33	Found in > 50% of tumors in women with invasive carcinoma of cervix; type 16 is found in 80% of men and women with bowenoid papulosis of external genital lesions usually disappear spontaneously, but future cancers may appear
2, 5, 11, 16	Buschke-Löwenstein giant condyloma is often malignant; also found in cervical dysplasia and laryngeal tumors
16	Most are associated with cervical intraepithelial neoplasia (see Ch. 241)
1	Common warts, usually benign
2, 4	Often malignant; sunlight and x-ray therapy are cofactors, especially with type 5
7, 9, 10, 12, 14, 17-19, 20, 21-25	Most seem benign, except possibly 14, 17, and 20
others	Often malignant; sunlight is a cofactor
16, 30	May become malignant; may occur in infants on passage through the vaginal canal and in adults as a consequence of oral-genital sex; may spread to lungs as cancer
	Benign

2) or a 5% ed sequen-uoroumcel to treat flat may follow exions.

long-term n are avall-njection of bleomycin and cures reports of

Raynaud's phenomenon and vascular damage of fingers where warts have been injected with bleomycin warrant extreme caution despite the popularity and effectiveness of this technique among some experts.

Extensive warts, even in hitherto untreatable epidermodysplasia verruciformis, have improved or cleared with oral isotretinoin or etretinate, which must be used by physicians familiar with these drugs and their possible adverse effects, especially fetal abnormalities during pregnancy.

Interferon, especially interferon- α , intravesically (3 times/wk for 3 to 5 wk) or IM, has also cleared intractable skin and genital warts.

MOLLUSCUM CONTAGIOSUM

A poxvirus infection characterized by skin-colored, smooth, waxy, umbilicated papules 2 to 10 mm in diameter.

Transmission, often venereal, is by direct contact. Numerous small papules may appear anywhere on the skin, often in the genital and pubic area. The lesions are usually asymptomatic, unless secondarily infected, and may be discovered when the patient is examined for a sexually transmitted disease.

Lesions can be diagnosed easily by the characteristic central umbilication or dell, filled with a semisolid white material that, if expressed and Giemsa-stained, shows inclusion bodies within many large cells or extracellularly. The disease can spread by autoinoculation but, after months, may disappear spontaneously. A giant molluscum may grow to two or three times its original diameter. Eczematous dermatitis may surround several mollusca, especially in young children; the cause is unknown.

Successful treatment usually requires destroying each lesion by freezing; by removing the central core of the papule with a needle, a comedo extractor, or the tip of a #11 scalpel blade; or by trichloroacetic acid application (25 to 40% solution).

116 / DISORDERS OF HAIR FOLLICLES AND SEBACEOUS GLANDS

ACNE

A common inflammatory disease of the pilosebaceous glands characterized by comedones, papules, pustules, inflamed nodules, superficial pus-filled cysts, and (in extreme cases) conicalizing and deep, inflamed, sometimes purulent sacs.

Pathogenesis

An interaction among hormones, keratin, sebum, and bacteria determines the course and severity. Acne usually begins at puberty, when an increase in androgens causes an increase in the size and activity of pilosebaceous glands. Inflammatory acne lesions include papules, pustules, and nodules or cysts. Noninflammatory lesions include open and closed comedones (ie, blackheads and whiteheads). First, intrafollicular hyperkeratosis leads to blockage of the pilosebaceous follicle; consequently, comedones form, composed of sebum, keratin, and microorganisms, particularly *Propionibacterium acnes*. Lipases from *P. acnes* break down triglycerides in the sebum to free fatty acids

(FFA), which irritate the follicular wall. Retention of sebaceous secretions and dilation of the follicle may lead to cyst formation. Rupture of the follicle, with release into tissues of FFA, bacterial products, and keratin, induces an inflammatory reaction that usually results in an abscess. These abscesses heal, with scarring in severe cases. Acne usually spontaneously remits, but the time of remittance cannot be predicted.

Symptoms and Signs

Acne is often worse in winter and improved in summer, probably because of the benefits of sunlight. Diet has little effect; however, if a food is suspected, it should be omitted for several weeks and then eaten in substantial quantities to determine if acne worsens. Acne may cycle with the menses, and it may improve or worsen during pregnancy. Although cosmetics rarely aggravate acne, the traditional advice to avoid greasy preparations seems prudent.

Superficial acne: Blackheads (open comedones) or whiteheads (closed come-

comedones, inflamed papules, pustules, and superficial cysts are characteristic. Large cysts occur occasionally, sometimes after manipulation or trauma to an otherwise uninfamed blackhead. The prognosis for healing without scars is good in superficial acne, but attempts to extrude blackheads or superficial cysts and scratching of ruptured lesions may increase scarring.

Deep acne: This form is characterized by the above findings with deep inflamed nodules and pus-filled cysts, which often rupture and become abscesses. Some of the abscesses open on the skin surface and discharge their contents. Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected. Scarring is frequent.

Diagnosis

Comedones are almost always present, and lesions at various stages of development are seen simultaneously. Differential diagnosis includes rosacea, which does not have comedones, and corticosteroid-induced acneiform lesions, which usually have follicular pustules in the same stage of development and no comedones.

Treatment

Although acne is almost universal, it may embarrass adolescents, who may withdraw, using the acne as an excuse to avoid difficult personal adjustments. Supportive counseling for patients and parents may be needed. Misconceptions about a relationship between acne and diet, athletics, or sex are common and warrant discussion. Treatment depends on the severity of the lesions.

Superficial acne: Although washing lesions several times a day has little effect, the appearance of an oily face often improves. Any good toilet soap may be used. Antibacterial soaps are of no benefit, and irritation from abrasive soaps makes it difficult to use follicular drugs (see below).

In superficial pustular acne, topical clindamycin or erythromycin alone or with one of the follicular drugs mentioned below is probably most useful. Sunlight causes mild dryness and slight scaling and is usually helpful. However, sunlight is not always available, and its benefit may be difficult to duplicate with a sunlamp. Azelaic acid cream 20%, which has antiproliferative and antibacterial

effects, may be effective in comedonal or inflammatory acne.

Topical tretinoin (retinoic acid) in 0.025%, 0.05%, or 0.1% cream, 0.05% liquid, or 0.01% or 0.025% gel is also often effective. A new topical retinoid, adapalene 0.1% gel, was recently approved in the USA. It may be slightly less irritating than topical tretinoin. These retinoids must be applied carefully and at night (every other night if irritation is excessive), going over the entire affected area only once. The eyes, nasolabial folds, and creases of the mouth should be avoided. The liquid form of tretinoin should be applied with a cotton-tipped applicator. Exposure to sunlight and use of other drugs are restricted to prevent severe irritation. With tretinoin or adapalene, acne may worsen at first; improvement usually requires ≥ 3 to 4 wk.

Other topical drugs include 5% to 10% benzoyl peroxide, OTC drugs, and various sulfur-resorcinol combinations; they are usually applied twice daily or one preparation at night and another in the morning. Oral antibiotics may also be helpful in superficial pustular acne.

Deep acne: Vigorous management is required to reduce residual scarring. For severe, deep lesions, topical treatment is unsatisfactory; a broad-spectrum oral antibiotic is usually effective because it reduces bacterial organisms. The most cost-effective is tetracycline; 250 mg qid or 500 mg bid (between meals and at bedtime) should be continued for ≥ 4 wk and then decreased to the lowest effective dose. Occasionally the dosage must be increased to 500 mg qid. Because relapse ordinarily follows short-term treatment, therapy must be continued for months to years, although tetracycline 250 or 500 mg/day is often sufficient. Many dermatologists consider the more costly minocycline to be the systemic antimicrobial of choice because of its efficacy, lack of GI side effects, simplified dosing with regard to meals, and lack of photosensitization. Side effects include dizziness and pigmentation of the skin and mucous membranes. Other systemic antimicrobials that may be used include erythromycin and doxycycline. Both can cause GI side effects, and doxycycline is a frequent photosensitizer. Tetracycline should not be given at bedtime because of the risk of esophageal erosions. Full-dose systemic antibiotics (tetracycline 500 mg bid, minocycline 100 mg

bid, doxycycline 100 mg bid, and erythromycin 333 mg tid) should be continued ≥ 4 wk before tapering. Optimal therapeutic results are achieved in 6 to 12 wk.

The most common adverse effect of prolonged antibiotic use in women is candidiasis. If local and systemic therapy do not eradicate this problem, antibiotic therapy for acne must be stopped. Long-term use of antibiotics may also produce a granulomatous pustular folliculitis around the nose and in the center of the face. This uncommon superinfection may be difficult to clear; it is best treated with oral isotretinoin after continuing the oral antibiotic.

Oral isotretinoin is the best treatment for patients in whom antibiotics are unsuccessful or in patients with very severe deep acne. This drug has revolutionized therapy for acne but should be used only by physicians who are familiar with its adverse effects. Because isotretinoin is teratogenic, women at risk of pregnancy must use methods of contraception for 1 mo before taking the drug, while taking the drug, at least 1 mo after discontinuing it. Pregnancy tests before beginning therapy and monthly intervals are still recommended.

The dosage of isotretinoin is usually mg/kg/day for 20 wk. In recalcitrant cases, the dosage may be increased to 2 mg/day. If side effects make this dosage intolerable, it may be reduced to 0.5 mg/kg/day. After therapy, acne may continue to improve. Most patients do not require a second course of treatment; when needed, it may be resumed only after the drug has been stopped for 4 mo. Retreatment is required more often if the initial dosage is low (mg/kg/day). With this dosage (which is popular in Europe), fewer side effects occur; however, prolonged therapy is usually required.

Side effects occur in virtually all patients; the most common are dryness of conjunctivae and mucosae of the genitalia, chapped lips. Petrolatum usually alleviates mucosal and cutaneous dryness. Musculoskeletal symptoms (pain or stiffness of joints or of the lower back) occur in $\approx 15\%$ of patients. CBC, liver function, and glyceride and cholesterol levels should be determined before treatment. Except for CBC, each should be reassessed at 4 wk unless abnormalities are noted, need not be repeated until the end of treatment. Tr

active in comedonal or retinoic acid) in 0.025%, 0.05% liquid, or 0.1% gel, was often effective. A new retinoic acid 0.1% gel, was effective in the USA. It may be slightly more effective. These should be applied carefully and at night if irritation is excessive. Irritated areas only should be avoided. The liquid should be applied with a cotton swab. Exposure to sun should be avoided. Drugs are restricted to topical. With tretinoin or isotretinoin, the drug may worsen at first; it requires 3 to 4 wk. It includes 5% to 10% benzoyl peroxide, and various salicylic acids; they are usually used in one preparation at night or one preparation at the morning. Oral antibiotics are helpful in superficial pustular

management is residual scarring. For severe, topical treatment broad-spectrum oral antibiotics are effective because of resistance. The most common is 250 mg qid or 500 mg bid and at bedtime for 4 wk and then at effective dose. Dose must be increased to relapse ordinarily. Relapse, therapy must be to years, although relapse/day is often sufficient. Dermatologists consider the drug to be the systemic because of its effects, simplified dosing, and lack of photoeffects include dizziness, dry skin and mucous membrane antimicrobials, erythromycin and cause GI side effects, frequent photosensitivity should not be given at the risk of esophageal damage. Systemic antibiotics (tetracycline 100 mg

bid, doxycycline 100 mg bid, and erythromycin 333 mg tid) should be continued for 4 wk before tapering. Optimal therapeutic results are achieved in 6 to 12 wk.

The most common adverse effect of prolonged antibiotic use in women is candidal vaginitis. If local and systemic therapy does not eradicate this problem, antibiotic therapy for acne must be stopped. Long-term use of antibiotics may also produce a gram-negative pustular folliculitis around the nose and in the center of the face. This uncommon superinfection may be difficult to clear and is best treated with oral isotretinoin after discontinuing the oral antibiotic.

Oral isotretinoin is the best treatment for patients in whom antibiotics are unsuccessful or in patients with very severe deep acne. This drug has revolutionized therapy for acne but should be used only by physicians who are familiar with its adverse effects. Because isotretinoin is teratogenic, women at risk of pregnancy must use two methods of contraception for 1 mo before taking the drug, while taking the drug, and at least 1 mo after discontinuing it. Pregnancy tests before beginning therapy and at monthly intervals are still recommended.

The dosage of isotretinoin is usually 1 mg/kg/day for 20 wk. In recalcitrant cases, the dosage may be increased to 2 mg/kg/day. If side effects make this dosage intolerable, it may be reduced to 0.5 mg/kg/day. After therapy, acne may continue to improve. Most patients do not require a second course of treatment; when needed, it should be resumed only after the drug has been stopped for 1 mo. Re-treatment is required more often if the initial dosage is low (0.5 mg/kg/day). With this dosage (which is very popular in Europe), fewer side effects occur; however, prolonged therapy is usually required.

Side effects occur in virtually all patients; the most common are dryness of conjunctivae and mucosae of the genitalia and chapped lips. Petrolatum usually alleviates mucosal and cutaneous dryness. Musculoskeletal symptoms (pain or stiffness of large joints or of the lower back) occur in about 15% of patients. CBC, liver function, and triglyceride and cholesterol levels should be determined before treatment. Except for the CBC, each should be reassessed at 4 wk and, unless abnormalities are noted, need not be repeated until the end of treatment. Triglyc-

erides rarely increase to a level at which the drug should be discontinued. Liver function is seldom affected.

For firm (cystic) acne lesions, injection of 0.1 mL triamcinolone acetonide suspension 2.5 mg/mL (the 10 mg/mL suspension must be diluted) into an inflamed cyst or abscess is helpful; local atrophy (resulting from the corticosteroid or destruction of tissue by the cyst) is usually transient. For isolated, very boggy lesions, incision and drainage are often beneficial but may result in residual scarring.

Dermabrasion for small scars is sometimes useful, but its permanent effect is controversial. X-ray therapy is not justified. Topical corticosteroids, especially if fluorinated, may worsen acne. When other measures fail and acne seems related to menses, an oral estrogen-dominant estrogen-progesterone-containing contraceptive may be tried; therapy 6 mo is needed to evaluate the effect.

ROSACEA

A chronic inflammatory disorder, usually beginning in middle age or later and characterized by telangiectasia, erythema, papules, and pustules primarily in the central areas of the face.

Tissue hypertrophy, particularly of the nose (rhinophyma), may result. Rarely, rosacea occurs on the trunk and extremities.

The cause is unknown, but the disease is most common in persons with a fair complexion. Diet probably plays no role in the pathogenesis. Rosacea may resemble acne, but comedones are never present; differential diagnosis also includes drug eruptions (particularly from iodides and bromides), granulomas of the skin, lupus erythematosus, and perioral dermatitis.

Treatment

Topical metronidazole gel or cream or broad-spectrum oral antibiotics are usually effective. Tetracycline 1 g/day in divided doses (between meals and in the evening) is most effective and has few side effects with long-term use. The dose should be reduced once a beneficial response is achieved. Often, 250 mg/day or every other day controls the disease. If tetracycline is ineffective or not tolerated, minocycline, erythromycin, and doxycycline are effective alternatives.

